PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PG3600/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/07303	05/10/1999	23/12/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19/07/2000	10.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Loubradou-Bourges, N Telephone No. +49 89 2399 7342

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07303

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-23 as originally filed

Claims, No.:

1-20 as originally filed

Drawings, sheets:

1/15-15/15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 12-15.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 12-15.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims

	No:	Claims	1-11, 16-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11, 16-20
Industrial applicability (IA)	Yes:	Claims	1-11, 16-17, 19-20
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1: WO 98 18921 A (HUMAN GENOME SCIENCES INC ;NI JIAN (US); EBNER REINHARD (US); YU G) 7 May 1998 (1998-05-07)
D2: EP-A-0 869 180 (SMITHKLINE BEECHAM CORP) 7 October 1998 (1998-10-07)
D3: WO 98 27114 A (SCHERING CORP) 25 June 1998 (1998-06-25)
D4: WO 98 55620 A (MASIAKOWSKI PIOTR ;REGENERON PHARMA (US); VALENZUELA DAVID (US)) 10 December 1998 (1998-12-10)
D5: WO 98 55621 A (MASIAKOWSKI PIOTR ;REGENERON PHARMA (US); VALENZUELA DAVID (US)) 10 December 1998 (1998-12-10)
D6: GRUSS H -J-: 'Molecular, structural, and biological characteristics of the tumor necrosis factor ligand superfamily' INTERNATIONAL JOURNAL OF CLINICAL AND LABORATORY RESEARCH,DE,SPRINGER, BERLIN, vol. 26, no. 3, 1996, pages 143-159, XP002094504 ISSN: 0940-5437

RE ITEM V

1. The present application does not meet the requirement of Article 33(2) since claims 1-11, 16-20 are not novel:

1.1 D1-D5 relate to TNF protein family members proteins which are closely related to the disclosed protein of the invention. As for example, the protein of D1 named Neutrokine α differs from the amino acid sequence shown in Seq ID N°1 only in that a E amino acid in Neutrokine α is replaced by a G amino acid at position 126 of the Seq ID N°1. Therefore, said TNF members proteins of D1-D5 are considered to be variants of the so-called soluble D7 ligand of the invention, and are prejudicial to the novelty of **claim 1(ii)**.
The same reasoning applies to **claim 2** since SEQ ID N°2 merely represents the entire form of D7 ligand and therefore its variant is anticipated by the complete amino acid sequence of Neutrokine α.

1.2 The Neutrokine α polypeptide of D1 is 99.3% homologous to the amino acid sequence of Seq ID N°1. Thus, **claim 3** is not novel.

1.3 The trimeric structure is the standard structure of TNF ligand superfamily (see D6). Therefore, **claims 4-5** are considered to be merely the description of inherent and known properties of the claimed proteins and therefore lack novelty.

1.4 D1-D5 relate to the polynucleotides corresponding to the TNF ligand proteins, corresponding vectors, host cells and antibodies. Thus, **claims 6-10** are not novel.

1.5 D1 (p.54-57) provides a method of screening compounds to identify those which enhance or block the action of Neutrokine α on cells, comprising contacting Neutrokine α bound to the receptor with the potential agonist or antagonist compound and providing an assay for determining the effect of said potential agonist or antagonist on Neutrokine α. Thus, the subject-matter of **claim 11** is not novel.

1.6 D1 (p.48-50) relates to the use of Neutrokine α to treat different diseases as for example disorders of the immune system, angiogenesis, etc. Therefore, the subject-matter of **claims 16-18** is not novel.

1.7 D1 (p.26-28) relates to the production of Neutrokine α polypeptides or fragment thereof by recombinant standard techniques, Thus, the subject-matter of **claim 19** is not new.
Claim 20 do not add any additional feature which permits to render said claim novel since the trimer form is the standard structure of the TNF-like proteins and thus is an inherent characteristic (see also 1.3).

2. The present application does not meet the requirement of Art. 33(3) PCT since claims 1-11, 16-20 lack inventive step for the following reasons:
D1 which is considered to be the closest prior art discloses a polypeptide of the well-known TNF ligand superfamily. The problem underlying the present application can be considered as the mere provision of a variant of the polypeptide of D1. The solution proposed consists in the provision of the

sequences shown in Seq ID N°1 and 2. The only difference between the presently claimed molecule and Neutrokine α is at position 258 of the entire sequence (E[SPEC05d5]G). However, in the absence of particular or unexpected effect provided by said differences, this solution does not involve an inventive step and is considered to be easily arrived at to a skilled person in the art. Therefore, the subject-matter of **claims 1-2** is not inventive.
Correspondingly, **claims 3-11, 16-20** which are merely derived products of Seq ID N°1 and 2 and methods of use thereof do not involve an inventive step.

3. For the assessment of the present claim 18 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

RE ITEM VIII

The present application does not meet the requirement of Article 6 PCT since claims 1-11, 16-20 are not clear for the following reasons:

1. The term "variant" of a polypeptide employed in claim 1(ii) is vague and indefinite, thus leaving the reader in doubt as to the meaning of the technical features to which it refers. Correspondingly, claims 2-11, 16-20 which refer to claim 1 are also unclear.

2. The term "variant" of a polynucleotide employed in claim 7 is vague and indefinite and may encompass any polynuleotide sequence.

3. In the absence of reference point, the expressions "modulates the interaction", "monitoring the modulation" employed in claim 11 is unclear.

4. The expression "monitoring for modulation of interaction" in claim 7 is unclear since it leaves the skilled reader in doubt as to the meaning of technical features to which it refers.

5. The definition of a disorder which is "responsive to modulation of.." in claim 18 is vague and indefinite.

6. The antibody of claim 10 is considered to be not supported by the description since in view of the very high degree of homologies between the claimed amino acid sequences and the sequence of TNF ligands present in the prior art (more than 99%), a specific antibody is not deemed to be obtainable.